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(54) Title: DRY GRANULATED FORMULATIONS OF AZITHROMYCIN

(57) Abstract: This invention relates to a pharmaceutical formulation, in the form of a tablet, sachet or powder for suspension dosage form, which comprises dry granulated particles of a non-dihydrate form of azithromycin and, optionally, one or more pharmaceutically acceptable excipients. Preferably, the pharmaceutical formulation is a tablet containing between about 40%, by weight, to about 85%, by weight, non-dihydrate azithromycin. More preferably, the pharmaceutical formulation contains non-dihydrate azithromycin selected from the forms B, D, E, F, G, H, J, M, N, O, P, Q, R, or mixtures thereof. Even more preferably, the invention relates to a pharmaceutical formulation wherein the dosage of azithromycin is 250 mgA, 500 mgA, 600 mgA or 1000 mgA. The present invention further relates to a dry granulated azithromycin particle, comprising a form of azithromycin, selected from forms D, E, F, G, H, J, M, N, O, P, Q, R and mixtures of non-dihydrate forms, and at least one pharmaceutically acceptable excipient.

DRY GRANULATED FORMULATIONS OF AZITHROMYCIN

## BACKGROUND OF THE INVENTION

5           Dry granulation is a process in which granulates are formed by a compaction step that is followed by sizing the compacts into particles that can be processed easily. It is often used to improve flow properties and/or densify the formulation which can facilitate  
10 further manufacturing processes such as tableting, encapsulation and powder filling. The compacts are made directly from powder blends that usually contain an active ingredient and other excipients including a lubricant.

15           Pharmaceutical manufacturers prefer the use of dry granulation techniques to wet granulation methods because of shorter processing times and cost advantages. However, dry granulation is generally limited to those situations in which the drug or active ingredient has  
20 physical characteristics suitable for forming pharmaceutically acceptable granulations and dosage forms such as tablets.

          The addition of at least one excipient to the formulation is generally required and will contribute to  
25 increasing the tablet size of the final product. As tablet size must be within certain parameters to function as a suitable dosage form, there is a limit beyond which increasing tablet size to accommodate increasing amounts of excipients to enhance  
30 compactability is not practical. As a result, manufacturers are often limited to using the dry granulation method for formulations containing a low

dose of the active ingredient per compressed tablet such that the formulation may accommodate sufficient levels of excipient to make dry granulation practical.

In the development of pharmaceutical dosage forms, it is important to balance several different objectives. It is important to prepare a pharmaceutical dosage form as economically as possible. It would be desirable to have a simple production method comprising a few processing steps. The dosage form should also optimally make available the active compound contained therein to the patient. Further, the dosage form should be easy to swallow. Smaller dosage forms are better accepted by patients and increase patient compliance.

Tablets are typically formed by pressure being applied to the material to be tableted on a tablet press. A formulation must have good flow properties for precise volumetric feeding of the material to the die cavity and suitable compressibility, compactability, and ejection properties to form a tablet.

There are a number of tablet presses, each varying in productivity but similar in basic function and operation. All compress a tablet formulation within a die cavity by pressure exerted between two steel punches, a lower punch and an upper punch. Tablet presses are typically designed to have a hopper for holding and feeding the formulation, a feeding mechanism for feeding the formulation to the die cavity, provision for placement of punches and dies, and in rotary tablet presses a cam track for guiding the movement of the punches. Two types of tablet presses are the single station or single-punch press and the multistation rotary press. Some tablet presses provide longer dwell

times than others, allowing increased bonding to occur.  
Other presses may provide precompression.

Azithromycin, which is also named 9-deoxo-9a-aza-9a-methyl-9a-homoerythromycin A, generally, is not  
5 considered to be amenable to the production of directly compressible tablets of azithromycin formulations.

It would be desirable to develop an azithromycin formulation that is amenable to form suitable granules by dry granulation methods or to form tablets, from  
10 these granules, that have acceptable hardness and friability.

#### SUMMARY OF THE INVENTION

This invention relates to a pharmaceutical  
15 formulation, in the form of a tablet, sachet or powder for suspension dosage form, which comprises dry granulated particles of a non-dihydrate form of azithromycin and, optionally, one or more pharmaceutically acceptable excipients. Preferably, the  
20 pharmaceutical formulation is a tablet containing between about 40%, by weight, to about 85%, by weight, non-dihydrate azithromycin.

More preferably, the pharmaceutical formulation contains non-dihydrate azithromycin selected from the  
25 forms B, D, E, F, G, H, J, M, N, O, P, Q, R, or mixtures thereof.

Even more preferably, the invention relates to a pharmaceutical formulation wherein the dosage of azithromycin is 250 mgA, 500 mgA, 600 mgA or 1000 mgA.

30 The present invention further relates to a dry granulated azithromycin particle, comprising

a form of azithromycin, selected from forms D, E, F, G, H, J, M, N, O, P, Q, R and mixtures of non-dihydrate forms, and at least one pharmaceutically acceptable excipient.

5

#### DETAILED DESCRIPTION

In the specification and claims that follow, reference will be made to a number of terms which shall be defined to have the following meaning.

10       The term "dry granulation" means the process of blending bulk azithromycin with at least one excipient. The blend is then compressed, or compacted, to form a compressed material or "compact". This material is then broken apart to form granules by crushing, grinding or  
15       cutting into dry granulated particles. Optionally, the particles may be further processed. Crushing, grinding, or cutting processes involve an operation that reduces the size of the compressed material such as accomplished by milling or by other operations known to those skilled  
20       in the art.

A "compact" is a compressed material formed by processing azithromycin and optional excipients by slugging or by roller compaction.

25       "Bulk azithromycin", as used herein, means azithromycin particles without added excipients. In the present invention, bulk azithromycin may be milled or unmilled.

30       "Granules", or "dry granulated particles" are defined herein as particles containing azithromycin and at least one pharmaceutically acceptable excipient, that are formed by dry granulation means.

The term "pharmaceutically acceptable" means that which is generally safe, non-toxic and neither biologically nor otherwise undesirable and includes that which are acceptable for human pharmaceutical use as well as veterinary use.

"Non-dihydrate azithromycin" means all amorphous and crystalline forms of azithromycin including all polymorphs, isomorphs, clathrates, salts, solvates and hydrates of azithromycin other than form A, the dihydrate form of azithromycin (azithromycin dihydrate).

Non-dihydrate azithromycin includes a hygroscopic hydrate of azithromycin, as disclosed in U.S. Patent 4,474,768, which is designated herein as "form B".

Preferably, azithromycin is present in several alternate crystalline non-dihydrate forms, including forms D, E, F, G, H, J, M, N, O, P, Q and R, which are disclosed in U.S. Patent Application Serial Number 10/152,106, filed 21 May 2002, the teachings of which are incorporated herein, by reference, in their entirety.

Both Family I and Family II isomorphs are hydrates and/or solvates of azithromycin. The solvent molecules in the cavities have a tendency to exchange between solvent and water under specific conditions. Therefore, the solvent/water content of the isomorphs may vary to a certain extent. Forms B, F, G, H, J, M, N, O, and P belong to Family I azithromycin and belong to a monoclinic  $P2_1$  space group with cell dimensions of  $a = 16.3 \pm 0.3 \text{ \AA}$ ,  $b = 16.2 \pm 0.3 \text{ \AA}$ ,  $c = 18.4 \pm 0.3 \text{ \AA}$  and  $\beta = 109 \pm 2^\circ$ . Forms D, E and R belong to Family II azithromycin and belong to an orthorhombic  $P2_1 2_1 2_1$  space group with

cell dimensions of  $a = 8.9 \pm 0.4 \text{ \AA}$ ,  $b = 12.3 \pm 0.5 \text{ \AA}$  and  $c = 45.8 \pm 0.5 \text{ \AA}$ . Form Q is distinct from Families I and II.

Form D azithromycin is of the formula  $C_{38}H_{72}N_2O_{12} \cdot H_2O \cdot C_6H_{12}$  in its single crystal structure, being  
5 azithromycin monohydrate monocyclohexane solvate. Form D is further characterized as containing 2-6% water and 3-12% cyclohexane by weight in powder samples. From single crystal data, the calculated water and cyclohexane content of form D is 2.1 and 9.9%,  
10 respectively.

Form E azithromycin is of the formula  $C_{38}H_{72}N_2O_{12} \cdot H_2O \cdot C_4H_8O$  being azithromycin monohydrate mono-tetrahydrofuran solvate. Form E is a monohydrate and mono-THF solvate by single crystal analysis.

15 Form G azithromycin is of the formula  $C_{38}H_{72}N_2O_{12} \cdot 1.5H_2O$  in the single crystal structure, being azithromycin sesquihydrate. Form G is further characterized as containing 2.5-6% water and <1 % organic solvent(s) by weight in powder samples. The  
20 single crystal structure of form G consists of two azithromycin molecules and three water molecules per asymmetric unit. This corresponds to a sesquihydrate with a theoretical water content of 3.5%. The water content of powder samples of form G ranges from about  
25 2.5 to about 6%. The total residual organic solvent is less than 1% of the corresponding solvent used for crystallization.

Form H azithromycin is of the formula  $C_{38}H_{72}N_2O_{12} \cdot H_2O \cdot 0.5C_3H_8O_2$  being azithromycin monohydrate  
30 hemi-1,2 propanediol solvate. Form H is a



monohydrate/hemi-propylene glycol solvate of azithromycin free base.

Form J azithromycin is of the formula  $C_{38}H_{72}N_2O_{12} \cdot H_2O \cdot 0.5C_3H_7OH$  in the single crystal structure, being azithromycin monohydrate hemi-n-propanol solvate. Form J is further characterized as containing 2-5% water and 1-5% n-propanol by weight in powder samples. The calculated solvent content is about 3.8% n-propanol and about 2.3% water.

Form M azithromycin is of the formula  $C_{38}H_{72}N_2O_{12} \cdot H_2O \cdot 0.5C_3H_7OH$ , being azithromycin monohydrate hemi-isopropanol solvate. Form M is further characterized as containing 2-5% water and 1-4% 2-propanol by weight in powder samples. The single crystal structure of form M would be a monohydrate/hemi-isopropanolate.

Form N azithromycin is a mixture of isomorphs of Family I. The mixture may contain variable percentages of isomorphs, F, G, H, J, M and others, and variable amounts of water and organic solvents, such as ethanol, isopropanol, n-propanol, propylene glycol, acetone, acetonitrile, butanol, pentanol, etc. The weight percent of water can range from 1-5.3% and the total weight percent of organic solvents can be 2-5% with each solvent content of 0.5 to 4%.

Form O azithromycin is of the formula  $C_{38}H_{72}N_2O_{12} \cdot 0.5H_2O \cdot 0.5C_4H_9OH$ , being a hemihydrate hemi-n-butanol solvate of azithromycin free base by single crystal structural data.

Form P azithromycin is of the formula  $C_{38}H_{72}N_2O_{12} \cdot H_2O \cdot 0.5C_5H_{12}O$  being azithromycin monohydrate hemi-n-pentanol solvate.

Form Q azithromycin is of the formula  $C_{38}H_{72}N_2O_{12} \cdot H_2O \cdot 0.5C_4H_8O$  being azithromycin monohydrate hemi-tetrahydrofuran solvate. It contains about 4% water and about 4.5% THF.

5        Form R azithromycin is of the formula  $C_{38}H_{72}N_2O_{12} \cdot H_2O \cdot C_5H_{12}O$  being azithromycin monohydrate mono-methyl tert-butyl ether solvate. Form R has a theoretical water content of 2.1 weight % and a theoretical methyl tert-butyl ether content of 10.3  
10    weight %.

Form F azithromycin is of the formula  $C_{38}H_{72}N_2O_{12} \cdot H_2O \cdot 0.5C_2H_5OH$  in the single crystal structure, being azithromycin monohydrate hemi-ethanol solvate. Form F is further characterized as containing 2-5% water  
15    and 1-4% ethanol by weight in powder samples.

The single crystal of form F is crystallized in a monoclinic space group,  $P2_1$ , with the asymmetric unit containing two azithromycin, two waters, and one ethanol, as a monohydrate/hemi-ethanolate. It is isomorphic to  
20    all Family I azithromycin crystalline forms. The theoretical water and ethanol contents are 2.3 and 2.9%, respectively.

The term "mgA" refers to milligrams of the free base of azithromycin.

25        The term "blend", as used herein, means a generally homogeneous mixture of non-dihydrate azithromycin and at least one pharmaceutically acceptable excipient in particle form. The particles may be in powdered form or, alternatively, larger aggregated or agglomerated  
30    particles. The non-dihydrate azithromycin in a blend, of the present invention, is selected from azithromycin

forms D, E, F, G, H, J, M, N, O, P, Q, R or mixtures of non-dihydrate forms.

The blend, of the present invention, is used to produce non-dihydrate azithromycin granules by dry granulation methods such as by compressing or compacting. Typically, blends of the present invention, include up to about 99 wt% non-dihydrate azithromycin, from about 0 wt% to about 90 wt% binder, from 0 wt% to about 85 wt% diluent, from 0 wt% to about 15 wt% disintegrant; and from about 0.25 wt% to about 10 wt% lubricant.

In a further embodiment, the dry blend contains up to about 80 wt% azithromycin, from about 2 wt% to about 10 wt% disintegrant, from about 0.5 wt% to about 8 wt% lubricant; and from about 0 wt% to about 85 wt% diluent.

Preferably, the azithromycin in the blend is azithromycin form F.

In the blend of the present invention, suitable pharmaceutically acceptable excipients include, but are not limited to, binders, diluents, disintegrants, lubricants, fillers, carriers, and the like.

Binders are used to impart cohesive qualities to a tablet formulation, and thus ensure that a tablet remains intact after compaction. Suitable binder materials include, but are not limited to, microcrystalline cellulose, gelatin, sugars (including sucrose, glucose, dextrose and maltodextrin), polyethylene glycol, waxes, natural and synthetic gums, polyvinylpyrrolidone, cellulosic polymers (including hydroxypropyl cellulose, hydroxypropyl methylcellulose, methyl cellulose, hydroxyethyl cellulose, and the like).

The diluent employed in a composition of the present invention may be one or more compounds which are capable of providing compactability and good flow. A variety of materials may be used as fillers or diluents.

5     Suitable diluents or fillers include, but are not limited to, lactose (monohydrate, spray-dried monohydrate, anhydrous and the like), sucrose, dextrose, mannitol, sorbitol, starch, cellulose (e.g. microcrystalline cellulose; Avicel), dihydrated or  
10     anhydrous dibasic calcium phosphate, calcium carbonate, calcium sulfate, and others as known in the art.

The preferred diluents are anhydrous lactose, lactose monohydrate and dibasic calcium phosphate. More preferably, the diluent is microcrystalline cellulose.

15     Many excipients, in the present invention, function as both a binder and a diluent, such a microcrystalline cellulose.

Lubricants can be employed herein in the manufacture of certain dosage forms, and will usually be  
20     employed when producing granules and tablets. In the present invention, a lubricant is typically added just prior to slugging or compacting to form the granule, and is mixed with the formulation for a minimum period of time to obtain good dispersal. The lubricant employed  
25     in the present invention may be one or more compounds. Examples of suitable lubricants include, but are not limited to, magnesium stearate, calcium stearate, zinc stearate, stearic acid, talc, glyceryl behenate, polyethylene glycol, polyethylene oxide polymers (for  
30     example, available under the registered trademarks of Carbowax for polyethylene glycol and Polyox for polyethylene oxide from Union Carbide, Inc., Danbury,

Conn.), sodium lauryl sulfate, magnesium lauryl sulfate, sodium oleate, sodium stearyl fumarate, DL-leucine, colloidal silica, and others as known in the art.

Preferred lubricants are magnesium stearate and mixtures  
5 of magnesium stearate with sodium lauryl sulfate. Lubricants may comprise from about 0.1 wt% to about 8.0 wt% of the granule weight.

Disintegrants are used to facilitate tablet disintegration or "breakup" after administration, and  
10 are generally starches, clays, celluloses, alginates, gums or crosslinked polymers. Suitable disintegrants include, but are not limited to, crosslinked polyvinylpyrrolidone (PVP-XL), sodium starch glycolate, and croscarmellose sodium. If desired, the  
15 pharmaceutical formulation may also contain minor amounts of nontoxic auxiliary substances such as wetting or emulsifying agents, pH buffering agents and the like, for example, sodium acetate, sorbitan monolaurate, triethanolamine sodium acetate, triethanolamine oleate,  
20 sodium lauryl sulfate, dioctyl sodium sulfosuccinate, polyoxyethylene sorbitan fatty acid esters, etc.

To prepare the blend, the various components may be weighed, delumped. The mixing may be carried out for a sufficient period of time to produce a homogeneous  
25 blend. Lubricant may be added in one, or multiple steps, prior to and/or after initial blending of the azithromycin and other excipients. Afterwards, the final mixing may be carried out. The blend may be stored for later use or formulated into a granule.

30 The components of the blend, including the non-dihydrate azithromycin and the excipient(s), may be combined by blending, mixing, stirring, shaking,

tumbling, rolling or by any other methods of combining the formulation components to achieve a homogeneous blend. It is preferable that the azithromycin and excipients are combined under low shear conditions in a  
5 suitable apparatus, such as a V-blender, tote blender, double cone blender or any other apparatus capable of functioning under preferred low shear conditions. Lubricant is typically added in the last step.

The invention should not be considered limited to  
10 these particular conditions for combining the components and it will be understood, based on this disclosure that the advantageous properties can be achieved through other conditions provided the components retain their basic properties and substantial homogeneity of the  
15 blended formulation components of the formulation is otherwise achieved without any significant segregation.

In one embodiment for preparing the blend, the components are weighed and placed into a blending container. Blending is performed for a period of time  
20 to produce a homogenous blend using suitable mixing equipment. Optionally, the blend is passed through a mesh screen to delump the blend. The screened blend may be returned to the blending container and blended for an additional period of time. Lubricant may then be added  
25 and the blend mixed for an additional period of time.

The blend, of the present invention, is then compressed, or compacted, to form a compact. Prior to compression, the blend may be subjected to a precompression step such as on a rotary tablet press.

30 Compression of the blend to form granules may be accomplished by techniques known in the art including slugging where the blend is introduced into dies

comprising one or more punch faces that are installed on a press such as a tablet press and pressure is applied to the blend by the movement of one or more punch faces in the die. Dry granulation may also be performed through the use of a roller compactor. A roller compactor generally incorporates two or more rollers adjacent and parallel to each other with a fixed or adjustable gap between the rollers. A hopper or other feeding device deposits blend between the moving rollers which act to compact the blend into a compacted material. Roller compactors are typically equipped with dividers that cut or otherwise divide the compacted material emerging from the roller compactor into ribbons. An example of a roller compactor is TF-Mini Roller Compactor (Vector Corporation, Marion, IA, Freund).

The compact is then broken apart to form granules, typically by suitable mechanical means, such as by crushing, grinding or cutting.

For example, granules may be formed from a compact by milling. Milling involves subjecting the granules to a shear force such that the desired particle size of the granulation is achieved. The milling step may range from an aggressive process where the particle size is reduced significantly to a non-aggressive process where the particle size is not reduced significantly, but merely done to delump or break up larger clumps of granulation.

In the pharmaceutical industry, milling is often used to reduce the particle size of solid materials. Many types of mills are available including pin mills, hammer mills and jet mills. One of the most commonly

used types of mill is the hammer mill. The hammer mill utilizes a high-speed rotor to which a number of fixed or swinging hammers are attached. The hammers can be attached such that either the knife face or the hammer  
5 face contacts the material. As material is fed into the mill, it impacts on the rotating hammers and breaks up into smaller particles. A screen is located below the hammers, which allows the smaller particles to pass through the openings in the screen. Larger particles are  
10 retained in the mill and continue to be broken up by the hammers until the particles are fine enough to flow through the screen. The material may optionally be screened. In screening, material is placed through a mesh screen or series of mesh screens to obtain the  
15 desired particle size.

The non-dihydrate azithromycin granules, of the present invention, which contain an azithromycin form selected from forms D, E, F, G, H, J, M, N, O, P, Q, R or mixtures of non-dihydrate forms, are then used to  
20 form a pharmaceutical formulation which is typically in the dosage form of a tablet, a capsule, a sachet or a powder for suspension.

Alternately, a pharmaceutical formulation of the present invention, comprising a tablet, sachet or powder  
25 for suspension, may consist of dry granulated particles of azithromycin form B and, optionally, at least one pharmaceutically acceptable excipient. The azithromycin form B granules can be made by the methods described for making the non-dihydrate azithromycin granules of the  
30 present invention.

Optionally, prior to forming the dosage form, the azithromycin granules are extragranularly mixed with at



least one additional pharmaceutically acceptable excipient, such as a processing aid (e.g., a lubricant or glidant) to form a pharmaceutical composition of the present invention. This pharmaceutical composition may  
5 then be tableted, encapsulated or packaged as a sachet or powder for oral suspension. Disintegrants, as are typically known in the art, and preferably as described herein, may also be added prior to tableting.

Flavors and coloring agents may be added, as  
10 excipients, intragranularly and/or extragranularly in the present invention.

Flavors incorporated in the composition may be chosen from synthetic flavor oils and flavoring aromatics and/or natural oils, extracts from plants  
15 leaves, flowers, fruits, and so forth and combinations thereof. These may include cinnamon oil, oil of wintergreen, peppermint oils, clove oil, bay oil, anise oil, eucalyptus, thyme oil, cedar leaf oil, oil of nutmeg, oil of sage, oil of bitter almonds, and cassia  
20 oil. Also useful as flavors are vanilla, citrus oil, including lemon, orange, grape, lime and grapefruit, and fruit essences, including apple, banana, pear, peach, strawberry, raspberry, cherry, plum, pineapple, apricot, and so forth. The amount of flavoring may depend on a  
25 number of factors including the organoleptic effect desired. Generally the flavoring will be present in an amount of from 0.5 to about 3.0 percent by weight based on the total dosage form weight, when a flavor is used.

Other excipients and coloring agents may also be  
30 added to azithromycin pharmaceutical formulations. Coloring agents include, but are not limited to, titanium dioxide and/or dyes suitable for food such as

those known as F. D. & C, dyes, aluminum lakes and natural coloring agents such as grape skin extract, beet red powder, beta carotene, annato, carmine, turmeric, paprika, and so forth. A coloring agent is an optional  
5 ingredient in the compositions of this invention, but when used will generally be present in an amount up to about 3.5 percent based on the total dosage form weight.

In one embodiment, the pharmaceutical formulation is a dosage form containing an amount of azithromycin  
10 equivalent to about 250 mgA. In a further embodiment the dosage form contains an amount of azithromycin equivalent to about 500 mgA. In yet another embodiment, the dosage form contains an amount of azithromycin equivalent to about 600 mgA. In an alternate  
15 embodiment, the dosage form contains an amount of azithromycin equivalent to about 1000 mgA.

Preferably, tablets of the present invention contain from about 40 wt% to about 90 wt% azithromycin of the total tablet weight, preferably from about 45 wt%  
20 to about 80 wt% azithromycin; from about 0 wt% to about 60 wt% binder; from 0 wt% to about 60 wt% filler; from 0 wt% to about 15 wt% disintegrant; and from about 0.25 wt% to about 10 wt% lubricant. In a further embodiment, the pharmaceutical formulation may comprise up to about  
25 80 wt% azithromycin; from about 2 wt% to about 10 wt% of disintegrant; from about 0.5 wt% to about 8 wt% of lubricant; and from about 0 wt% to about 60 wt% of filler.

Tablets may be prepared using standard tableting  
30 equipment known in the industry as a gravity fed process, and with equipment having means to force feed the pharmaceutical formulation.

Typical compacting techniques for the preparation of a tablet utilizes a piston like device with three stages in each cycle 1) filling (adding the constituents of the tablet to the compression chamber including granulate and any extragranularly added excipient(s)) 2) compaction (forming the tablet) and 3) ejection (removing the tablet). The cycle is then repeated. A representative tablet press is a MANESTY EXPRESS 20 rotary press, manufactured by Manesty Machines Ltd., Liverpool, England, and many others are available. The method as defined in this aspect of the invention is not limited to any particular equipment, however. The equipment may be gravity fed or it may utilize means to force feed the lubricated blend into the die.

15 In one embodiment, a high speed tablet press may be used. In a further embodiment, a single station tableting press may be used. Flow of the blend on high speed tablet presses is very important to good weight control of the tablet. The use of a force feeder often improves tablet weight control for poorer flowing blends. Another common feature of high speed tablet presses is the ability to use precompression. Precompression taps the blend when the die is full with blend before the final compression step forms the  
20 tablet.  
25

Prior to tableting, additional lubricant may be mixed with the granules. Suitable lubricants are as previously described herein. Lubricants may comprise from about 0.5 wt% to about 10 wt% of the tablet weight, more preferably about 1.0 to about 8 wt%, and even more preferably from about 3 to about 7.5 wt%. Typically,

the amount of lubricant used depends, in part, on the particular lubricant that is chosen.

Though generally not required with dry granulated tablets, in an alternate embodiment the dry granulated  
5 tablet may comprise an amount of glidant that is less than about 3% by weight, based on the tablet weight. In a further embodiment, the direct compression tablet may comprise an amount of glidant that is less than about 1% by weight, based on the tablet weight. In an even  
10 further embodiment, the tablet may comprise an amount of glidant that is less than about 0.5% by weight, based on the weight of the glidant.

Suitable glidants include magnesium trisilicate, powdered cellulose, starch, talc, tribasic calcium  
15 phosphate, stearate salts and colloidal silicon dioxide. Most preferred glidants are talc, magnesium stearate and colloidal silicon dioxide.

Blending of the azithromycin granules and optional additional excipient(s), including lubricant, may be  
20 accomplished by the methods previously described herein.

Tablets, of the present invention, typically exhibit acceptable physical characteristics including good friability and hardness. The resistance of a tablet to chipping, abrasion or breakage under  
25 conditions of storage and transportation depends on its hardness and friability.

Friability is a standard test known to one skilled in the art. Friability is measured under standardized conditions by weighing out a certain number of tablets  
30 (generally 20 tablets or less), placing them in a rotating Plexiglas drum in which they are lifted during replicate revolutions by a radial lever, and then

dropped approximately 8 inches. After replicate revolutions (typically 100 revolutions at 25 rpm), the tablets are reweighed and the percentage of formulation abraded or chipped is calculated. The friability of the  
5 tablets, of the present invention, is preferably in the range of about 0% to 3%, and values about 1%, or less, are considered acceptable for most drug and food tablet contexts. Friability which approaches 0% is particularly preferred.

10 In the present invention, it was unexpectedly found that compacts, used to prepare granules, that were prepared from azithromycin form F, were physically harder than compacts made from other forms of non-dihydrate azithromycin. Thus, these azithromycin form F  
15 granules are preferred for preparing oral dosage forms such as tablets.

Further, it was found that dry granulated tablets, containing azithromycin form F granules, possess superior hardness and friability characteristics. Thus,  
20 tablets containing azithromycin form F are also preferred.

In the present invention, it was also unexpectedly found that tablets containing drug loadings of 40 wt% azithromycin or greater were more robust than tablets  
25 with drug loadings of less than 40 wt% azithromycin. Thus, is also preferred that tablets contain from about to about 85 wt% non-dihydrate azithromycin.

The tablets, of the present invention, may be any shape as long as the tablet is in a form that it may be  
30 administered orally and is not prone to capping or exceeds the desired friability. The tablets may be round, oblong, thick or thin, large or small in

diameter, flat or convex, scored or unscored, and imprinted. Typically, examples of tablet shapes include, but are not limited to, round, oval, modified oval or modified capsule shapes.

- 5           In one embodiment, the tablet may be a modified capsule shape containing about 250mgA azithromycin, about 450 mg total weight. In one embodiment, the dimensions of the aforementioned tablet are 0.26" x 0.53". In a further embodiment, the tablet may be an
- 10          oval shape containing about 500mgA azithromycin, about 900 mg total weight. In one embodiment, the dimensions of the tablet are 0.33" x 0.67". In an even further embodiment, the tablet may be a modified oval shape containing about 600mgA, about 1070 mg total weight. In
- 15          one embodiment, the dimensions of the aforementioned tablet are 0.41" x 0.75". A reference to tablet shapes can be found in fig. 25, page 51 of the Tableting Specification Manual, fourth edition, published by the American Pharmaceutical Association, Washington, DC,
- 20          1995; incorporated herein by reference in its entirety.

Due to the tensile strength of azithromycin form F, it is preferred that tablets, of any shape, be made from azithromycin form F as compared to using other forms of non-dihydrate azithromycin.

- 25           The tablets comprising less than 40 wt% of non-dihydrate azithromycin forms, other than F, based on the total weight of the tablet are preferably round to prevent tablet breakage.

- 30           If desired, the tablet may be coated. The reasons for coating a tablet may include masking the taste of the drug, making tablets easier to swallow, protection

against chipping during packaging, a barrier for moisture or light to improve product stability, and enhancing product appearance or recognition.

The coating process may include the use of a  
5 coating solution or suspension, usually aqueous that has acceptable viscosity for spraying and properties for it to adhere to the surface of the tablet when applied. During the coating process, the coating solution or suspension is atomized into fine droplets that come into  
10 contact with the tablet. As the droplets dry, a film is formed on the tablet which is the coating. There are several types of coating equipment used to coat tablets. One type is the pan coater in which tablets are rotated in a pan and coating solution is applied to the tablets  
15 as tablets tumble in the pan. Another coating process involves suspending the tablets in a column of air while the coating solution is sprayed onto the tablet (fluid bed process). One example of this is the Wurster column coating process. The tablet may be coated by any known  
20 process and the manner of application is not limited to any particular equipment.

The tablet coating(s) may be a white or colored Opadry® (Colorcon, West Point PA) suspension or a clear Opadry® solution. Alternatively a typical coating  
25 formulation would consist of a film forming polymer(s) such as hydroxypropyl methylcellulose (HPMC), hydroxypropyl cellulose (HPC), polyvinyl pyrrolidone (PVP) with additional ingredients such as plasticizers, opacifiers, colorants, and antioxidants. Sugar coating  
30 could also be used.

The pharmaceutical formulations of the present invention may be used for the treatment of bacterial or

protozoal infections. The term "treatment", as used herein, unless otherwise indicated, means the treatment or prevention of a bacterial or protozoal infection, including curing, reducing the symptoms of or slowing  
5 the progress of said infection.

As used herein, unless otherwise indicated, the term "bacterial infection(s)" or "protozoal infection(s)" includes bacterial infections and protozoal infections that occur in mammals, fish and  
10 birds as well as disorders related to bacterial infections and protozoal infections that may be treated or prevented by administering antibiotics such as the compound of the present invention. Such bacterial infections and protozoal infections and disorders  
15 related to such infections include, but are not limited to, the following: pneumonia, otitis media, sinusitis, bronchitis, tonsillitis, and mastoiditis related to infection by *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Staphylococcus aureus*, or *Peptostreptococcus* spp.; pharyngitis,  
20 rheumatic fever, and glomerulonephritis related to infection by *Streptococcus pyogenes*, Groups C and G streptococci, *Clostridium diphtheriae*, or *Actinobacillus haemolyticum*; respiratory tract infections related to  
25 infection by *Mycoplasma pneumoniae*, *Legionella pneumophila*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, or *Chlamydia pneumoniae*; uncomplicated skin and soft tissue infections, abscesses and osteomyelitis, and puerperal fever related to infection by  
30 *Staphylococcus aureus*, coagulase-positive staphylococci (i.e., *S. epidermidis*, *S. hemolyticus*, etc.), *Streptococcus pyogenes*, *Streptococcus agalactiae*,



- Streptococcal groups C-F (minute-colony streptococci),  
*viridans streptococci*, *Corynebacterium minutissimum*,  
*Clostridium spp.*, or *Bartonella henselae*; uncomplicated  
acute urinary tract infections related to infection by  
5 *Staphylococcus saprophyticus* or *Enterococcus spp.*;  
urethritis and cervicitis; and sexually transmitted  
diseases related to infection by *Chlamydia trachomatis*,  
*Haemophilus ducreyi*, *Treponema pallidum*, *Ureaplasma*  
*urealyticum*, or *Neisseria gonorrhoeae*; toxin diseases  
10 related to infection by *S. aureus* (food poisoning and  
Toxic shock syndrome), or Groups A, B, and C  
streptococci; ulcers related to infection by  
*Helicobacter pylori*; systemic febrile syndromes related  
to infection by *Borrelia recurrentis*; Lyme disease  
15 related to infection by *Borrelia burgdorferi*;  
conjunctivitis, keratitis, and dacrocystitis related to  
infection by *Chlamydia trachomatis*, *Neisseria*  
*gonorrhoeae*, *S. aureus*, *S. pneumoniae*, *S. pyogenes*, *H.*  
*influenzae*, or *Listeria spp.*; disseminated *Mycobacterium*  
20 *avium* complex (MAC) disease related to infection by  
*Mycobacterium avium*, or *Mycobacterium intracellulare*;  
gastroenteritis related to infection by *Campylobacter*  
*jejuni*; intestinal protozoa related to infection by  
*Cryptosporidium spp.*; odontogenic infection related to  
25 infection by *viridans streptococci*; persistent cough  
related to infection by *Bordetella pertussis*; gas  
gangrene related to infection by *Clostridium perfringens*  
or *Bacteroides spp.*; and atherosclerosis related to  
infection by *Helicobacter pylori* or *Chlamydia*  
30 *pneumoniae*. Bacterial infections and protozoal  
infections and disorders related to such infections that  
may be treated or prevented in animals include, but are

- not limited to, the following: bovine respiratory disease related to infection by *P. haem.*, *P. multocida*, *Mycoplasma bovis*, or *Bordetella* spp.; cow enteric disease related to infection by *E. coli* or protozoa (i.e., coccidia, cryptosporidia, etc.); dairy cow mastitis related to infection by *Staph. aureus*, *Strep. uberis*, *Strep. agalactiae*, *Strep. dysgalactiae*, *Klebsiella* spp., *Corynebacterium*, or *Enterococcus* spp.; swine respiratory disease related to infection by A. pleuro., *P. multocida*, or *Mycoplasma* spp.; swine enteric disease related to infection by *E. coli*, *Lawsonia intracellularis*, *Salmonella*, or *Serpulina hyodysenteriae*; cow footrot related to infection by *Fusobacterium* spp.; cow metritis related to infection by *E. coli*; cow hairy warts related to infection by *Fusobacterium necrophorum* or *Bacteroides nodosus*; cow pink-eye related to infection by *Moraxella bovis*; cow premature abortion related to infection by protozoa (i.e. neosporium); urinary tract infection in dogs and cats related to infection by *E. coli*; skin and soft tissue infections in dogs and cats related to infection by *Staph. epidermidis*, *Staph. intermedius*, coagulase neg. *Staph.* or *P. multocida*; and dental or mouth infections in dogs and cats related to infection by *Alcaligenes* spp., *Bacteroides* spp., *Clostridium* spp., *Enterobacter* spp., *Eubacterium*, *Peptostreptococcus*, *Porphyromonas*, or *Prevotella*. Other conditions that may be treated by the compounds and preparations of the present invention include malaria and atherosclerosis.
- Other bacterial infections and protozoal infections and disorders related to such infections that may be treated or prevented in accord with the method and compositions

of the present invention are referred to in J. P. Sanford et al., "The Sanford Guide To Antimicrobial Therapy," 26th Edition, (Antimicrobial Therapy, Inc., 1996).

5           The term "effective amount" means the amount of azithromycin which, when administered in - the present invention prevents the onset of, alleviates the symptoms of, stops the progression of, or eliminates a bacterial or protozoal infection in a mammal.

10           The term "mammal" is an individual animal that is a member of the taxonomic class Mammalia. The class Mammalia includes, for example, humans, monkeys, chimpanzees, gorillas, cattle, swine, horses, sheep, dogs, cats, mice and rats.

15           In the present invention, the preferred mammal is a human.

Typically, azithromycin, is administered in dosage amounts ranging from about 0.2 mg per kg body weight per day (mg/kg/day) to about 200 mg/kg/day in single or  
20       divided doses (i.e., from 1 to 4 doses per day), although variations will necessarily occur depending upon the species, weight and condition of the subject being treated and the particular route of administration chosen. The preferred dosage amount is from about 2  
25       mg/kg/day to about 50 mg/kg/day.

The azithromycin may be administered orally, or by other known means for administering azithromycin.

Although the foregoing invention has been described in some detail for purposes of illustration, it will be  
30       readily apparent to one skilled in the art that changes and modifications may be made without departing from the scope of the invention described herein.

## EXEMPLIFICATION

The present invention will be further illustrated by means of the following examples. It is to be understood, however, that the invention is not meant to be limited to the details described therein.

Excipients, used in the following examples, were obtained as follows.

Dicalcium phosphate anhydrous was obtained from Rhone-Poulenc Chemicals, Shelton, CT.

Dicalcium phosphate dihydrate (Emcompress®) was obtained from Penwest Pharmaceuticals Co., Patterson, NY.

Spray-dried Lactose, monohydrate (Fast Flo®) was obtained from Foremost Farms, Rothschild WI.

Lactose, anhydrous direct tableting grade was obtained from Quest, Norwich, NY.

Microcrystalline cellulose (Avicel® PH200) was obtained from FMC Biopolymer, Philadelphia, PA.

Croscarmellose sodium (Ac-Di-Sol®) was obtained from FMC Biopolymer, Philadelphia, PA.

Crospovidone (PVP-XL, Polyplasdone® XL) was obtained from International Specialty Products, Wayne, NJ.

Sodium starch glycolate (Explotab®) was obtained from Penwest Pharmaceuticals Co., Patterson, NY.

Corn Starch (Purity 21®) was obtained from National Starch & Chemical, Bridgewater, NJ.

Magnesium stearate was obtained from Mallinckrodt, Inc., St. Louis, MO.

Sodium lauryl sulfate was obtained from Aceto Corporation, Lake Success, NY.

Example 1Indices of Tableting Performance

Indices of tableting performance, for several  
5 azithromycin forms, were assessed to identify any  
mechanical deficiencies or attributes that may affect  
tablet formulation for these azithromycin forms. This  
assessment was performed in accordance with the  
procedures described in "Indices of Tableting  
10 Performance" H. E. N. Hiestand and D. P. Smith, Powder  
Technology 38 [1984] pp. 145-159.

Specifically, the Brittle Fracture Index, BFI, was  
calculated from the ratio of a material's regular  
tensile strength to its compromised tensile strength.  
15 Strain Index, SI, was determined from the dynamic  
indentation hardness test. Worst Case Bonding Index was  
determined by assessing the extent of particle bonding  
remaining after decompression assuming a very short  
compression dwell time and a plastic mechanism of  
20 particle separation during decompression.

Tableting Indices were determined for bulk  
azithromycin lots of six different crystalline forms,  
specifically forms N, M, G, A, F and J. Forms N, M and  
G were milled with a Fitzmill (Model JT, The Fitzpatrick  
25 Co., Elmhurst, IL) using a 0.027" screen and knives at  
high speed in an attempt to match the smaller particle  
size of milled Form A. Unmilled forms F and J were  
evaluated "as is" due to their relatively small particle  
sizes. The results of these assessments are shown in  
30 Table 1.

Table 1  
Indices of Tableting Performance

Azithromycin Form	Brittle Fracture Index (BFI)	Worst Case Bonding Index (BL <sub>w</sub> ) X 10 <sup>2</sup>	Strain Index (SI)	Tensile Strength Mpa
Form N	0.05	0.7	0.0044	0.75
Form M	0.10	1.0	0.0048	0.79
Form G	ND	0.8	0.0043	1.03
Form A	0.10	0.9	0.0044	0.99
Form F	0.37	0.9	0.0041	1.62
Form J	0.11	0.7	0.0043	0.69

ND = not determined

- 5 As shown above, the tableting indices were similar for forms N, M, G, A and J. The data suggest that the primary deficiencies of these materials in forming compacts are their low to moderate tensile strengths. This may be manifested as low tablet hardness values.
- 10 Furthermore, the brittle fracture indices indicated that bonds formed during compression will more likely survive decompression when the compact is ejected from the die. The differences between these lots were not significant. Thus, these lots would likely have a similar probability
- 15 of forming acceptable tablet formulations.

Form F, however, exhibited significantly different mechanical properties. It had a higher tensile strength value indicative of forming stronger bonds. This resulted in tablets with higher hardness values and

20 lower friability.

Example 2Dry Granulation of Azithromycin Forms

The impact of the blending process and the effect of azithromycin form on dry granulation was evaluated as follows.

Compacts (slugs) of azithromycin forms A, M and F formulations were prepared from a dry blend of 35.2 wt% azithromycin, 54.8 wt% dicalcium phosphate anhydrous as the diluent, 4.0 wt% croscarmellose sodium as the disintegrant, and 5.0 wt% magnesium stearate as the lubricant. The final 1.0 wt% magnesium stearate was added later just before tableting, for a total of 6.0 wt% lubricant.

The dry granulations were prepared by two different methods of blending. The long method blended 3 wt% of the lubricant with the drug, diluent and disintegrant in a Turbula Shaker-Mixer (Willy A. Bachofen AG Maschinenfabrik, Basel, Switzerland) mixer for 10 minutes. The blend was screened (20 mesh) and then blended another 10 minutes. An additional 2 wt% of lubricant was added and it was blended on the Turbula Shaker-mixer for 2 more minutes.

Alternatively a short blend method was used to minimize blend mixing with the lubricant. In this method the initial 10 minutes spent blending the drug, diluent, and disintegrant did not include the lubricant. After screening (20 mesh) and additional blending of 5 minutes, 5 wt% of the lubricant was added and blended for only 2 minutes in the Turbula Shaker-mixer.

A compaction simulator was used to compress the blends. The compaction simulator was designed as a single station tablet press in which the compression

dwel time can be adjusted to simulate different types of tablet presses. All the formulations were slugged on the compaction simulator configured as the Kilian RX-67 press with a dwell time of 0.3145 seconds using 3/4" round flat face tooling. The slugs were then comminuted using a Fitz mill with a 0.125" screen with knives forward and run at slow speed. The final amount of lubricant (1.0% magnesium stearate) was added to the dry granulation and blended for 2 minutes in the Turbula Shaker-mixer. The slugs were tested for hardness (kP scale), using a Schleuniger hardness tablet tester (Dr. Schleuniger Pharmatron AG, Solothurn, Switzerland). The results are shown in Table 2.

Carr's Compressibility Index was used to evaluate the flowability of the four dry granulations. Carr's Compressibility Index is a simple test to evaluate flowability by comparing both the initial and final (tapped) bulk volumes and the rate of packing down. A useful empirical guide to flow is given by Carr's compressibility index:

$$\text{Compressibility Index(\%)} = [(\text{tapped density} - \text{initial density}) / \text{tapped density}] \times 100$$

The Carr's Compressibility Index was measured by taking an initial density of a 15 gram sample in a 100 ml graduated cylinder. The sample was tapped 2000 times on a VanKel Tap Density Tester (Model 50-1200, Edison, NJ) and the tapped density of the 15 gram sample in the 100 ml graduated cylinder was taken. The procedure is described in Int. J. Pharm. Tech. & Prod. Mfr., 6(3) 10-16, 1985. The results are provided in Table 2.



Table 2  
Summary of Dry Granulations

Lot #	1	2	3	4
Drug Form	A	F	A	M
Blend method	Long	Long	Short	Short
Dry Blend density (g/cc)				
As Is	0.59	0.50	0.59	0.68
Tapped	1.05	0.88	1.04	1.08
Carr's Index	44%	43%	43%	36%
Avg Slug Weight	1480 mg	1499 mg	1495 mg	1506 mg
Slug Compression Force	40kN	42kN	39kN	43kN
Avg Slug Hardness	13.4 kP	22.4 kP	13.7 kP	10.9 kP
Avg Slug Thickness	0.132"	0.133"	0.134"	0.137"
Granulation density (g/cc)				
As Is	0.88	0.84	0.78	0.82
Tapped	1.19	1.07	1.14	1.14
Carr's Index	26%	22%	32%	28%

The dry granulations prepared by the long blend method resulted in good flow as shown by Carr's Index values of less than 28. The shorter blend method produced granules with poorer flow, having higher Carr's Index values.

All four formulations were compressed on the compaction simulator using either 0.344" x 0.688" oval

tooling, or ½" standard round concave (SRC) tooling. The tablets were tested for hardness (kP scale), using a Schleuniger hardness tablet tester (Dr. Schleuniger Pharmatron AG, Solothurn, Switzerland), and for

5 friability (100 rotations/4 minutes) using a Vanderkamp Friabulator Tablet Tester (Vankel, Cary, North Carolina, US). The tests results are provided in Tables 2A and 2B.

Table 2A

10 Summary of Dry Granulation Tablet Data  
Using the Long Blend Method

Run #	1	2	3
Lot#	1	1	2
Drug Form	A	A	F
Blend method	Long	Long	Long
Tooling	Oval	½" SRC	Oval
Dwell Time (sec)	0.1153	0.1153	0.1153
Avg Tab Weight	751 mg	747 mg	750 mg
Compression Force	13.5kN	9.6kN	19kN
Avg Tablet Hardness	9.0 kP	5.8 kP	10.3 kP
Avg Tablet Thickness	0.202"	0.195"	0.201"
Friability	2 of 5 tablets broke	1.30%	0.48%
Mean disintegration Time (sec)	15	NR	20

NR = Not Run

Table 2B

Summary of Dry Granulation Tablet Data  
Using the Shorter Blend Method

Run #	4	5	6	7
Lot #	3	3	4	4
Drug Form	A	A	M	M
Blend method	Short	Short	Short	Short
Tooling	Oval	Oval	Oval	Oval
Dwell Time (sec)	0.1153	0.1153	0.1153	0.1153
Avg Tab Weight	752 mg	749 mg	749 mg	749 mg
Compression Force	12kN	18.7kN	19.4kN	14kN
Avg Tab Hardness	6.8 kP	8.2 kP	8.4 kP	5.1 kP
Avg Tab Thickness	0.204"	0.201"	0.204"	0.208"
Friability	tablets capped	tablets capped	tablets capped	tablets capped

5        The better tablets, made from azithromycin Form A, were compressed using a ½ inch SRC tooling (Run #2). The oval shaped tablets broke during friability testing.

10        Using azithromycin form F (Run #3), good oval shaped tablets were made. As shown in Example 1 the tableting indices data indicated that Form F has better tensile strength than Forms A and M. Both the Form F slugs and tablets were harder.

The disintegration time was determined in distilled water at 37 °C using an Automatic Disintegration Tester

(Model ZT72, Erweka USA Inc, Milford, CT) for the long blend tablets. Even with extensive blending times with magnesium stearate, reasonably short disintegration times of 15 and 20 seconds were obtained.

- 5       Based upon the lower Carr's Index, the long blend method was used for the following examples.

### Example 3

#### Effect of Azithromycin Form and Low and High Drug

#### 10       Loading

The effects of drug form on dry granulation tablets were investigated using low and high drug loading formulations with forms A, F, J, and M. The long blend method and testing procedures as set forth in Example 2  
15       were used.

The low drug loading formulation contained 35.2 wt% azithromycin, 54.8 wt% dicalcium phosphate anhydrous, 4.0 wt% croscarmellose sodium, and 6.0 wt% magnesium stearate. The high drug loading formulation contained  
20       58.2 wt% azithromycin, 31.8 wt% dicalcium phosphate anhydrous, 4.0 wt% croscarmellose sodium, and 6.0 wt% magnesium stearate.

Slugs were made and tested for hardness (kP scale) as described in Example 2. The results for the low and  
25       high drug loading granulations are shown in Tables 3A and 3B, respectively.

The target hardness of ~12 kP was obtained with a much lower compaction force for the higher drug loading formulations indicative of the binding properties of the  
30       bulk drug. Form F had even greater binding properties as was shown by the tensile strength in Example 1. The low drug loading slugs made with comparable compression

force were harder for form F than with the other forms, A, J and M. Carr's Index was used to evaluate the flowability of the granulations. All granulations had a Carr's Index value of 30% or less providing acceptable flow on a tablet press.

Table 3A  
Summary of Low Drug Loading Dry Granulations

Lot #	1	2	3	4
Drug Form	A	F	J	M
Avg Slug Weight	1480 mg	1499 mg	1500 mg	1506 mg
Avg Slug Compression Force	39 kN	42 kN	41 kN	43 kN
Avg Slug Hardness	13 kP	22 kP	14 kP	11 kP
Avg Slug Thickness	0.132"	0.131"	0.134"	0.138"
Granulation Density (g/cc)				
As Is	0.89	0.84	0.87	0.82
Tapped	1.19	1.08	1.12	1.14
Carr's Index	26%	22%	22%	28%

Table 3B  
Summary of High Drug Loading Dry Granulations

Lot #	1	2	3
Drug Form	A	J	M
Avg Slug Weight	1498 mg	1501 mg	1501 mg
Avg Slug Compression Force	28 kN	18 kN	22 kN
Avg Slug Hardness	12 kP	11 kP	12 kP
Avg Slug Thickness	0.156"	0.197"	0.191"
Granulation Density (g/cc)			
As Is	0.67	0.67	0.71
Tapped	0.96	0.93	0.92
Carr's Index	30%	28%	23%

- 5 The dry granulations were compressed into tablets on the compaction simulator using oval shape (0.344" x 0.688" punches, target weight 750 mg) tooling for the low drug loading formulations and a modified capsule shape (0.262" x 0.531" punch, target weight 450 mg)
- 10 tooling for the high drug loading formulations. Tablet hardness and friability data were generated for the tablets as was done in Example 2. The tablet data are provided in Tables 3C and 3D for the low and high drug loading formulations, respectively.

Table 3C

## Summary of Low Drug Loading Dry Granulation Tablet Data

Lot #	1	2	3	4
Drug Form	A	F	J	M
Avg Weight (mg)	751	748	747	749
Avg Compresssion Force	14kN	19kN	15kN	19kN
Avg Hardness (kP)	9.0	10.3	9.1	8.4
Avg Thickness (in)	0.202	0.201	0.201	0.204
Friability (%)	Broken tablets	0.48	Broken tablets	NR

NR = Not Run

5

Table 3D

## Summary of High Drug Loading Dry Granulation Tablet Data

Lot #	1	2	3
Drug Form	A	J	M
Avg Weight (mg)	448	452	452
Avg Compresssion Force	5kN	4kN	5kN
Avg Hardness (kP)	6.2	6.5	6.1
Avg Thickness (in)	0.218	0.229	0.225
Friability (%)	0.50	0.38	0.45

- As shown in Table 3C, the oval shaped tablets made with drug forms A and J broke during friability testing.
- 10 The low drug loading formulation with drug form F showed good tablet friability and hardness consistent with its better tensile strength. All of the modified capsule shaped tablets made with the high drug loading

granulations resulted in acceptable tablet hardness and good tablet friability as shown in Table 3D.

#### Example 4

##### 5     Effect of Different Diluents on Dry Granulation Tablets

          The effect of different diluents on dry granulation tablets was investigated with both low and high drug loading formulations. Azithromycin forms A, F, G, and M were blended with diluents, dicalcium phosphate(DCP) anhydrous, dicalcium phosphate(DCP) dihydrate (Emcompress®), lactose (Fast Flo®), and microcrystalline cellulose (MCC) (Avicel® PH200). The same long blend method and testing procedures as set forth in Example 2 were used.

15           The low drug loading formulation contained 35.2 wt% azithromycin, 54.8 wt% diluent, 4.0 wt% croscarmellose sodium, and 6.0 wt% magnesium stearate. The high drug loading formulation contained 58.2 wt% azithromycin, 31.8 wt% diluent, 4.0 wt% croscarmellose sodium, and 6.0  
20 wt% magnesium stearate. Slugs were made and tested for hardness (kP scale), as described in Example 2. The results for the low and high drug loading granulations are shown in Tables 4A and 4B, respectively. The Carr's Index was less than or equal to 30% for all the  
25 granulations. DCP dihydrate resulted in the lowest values, followed by MCC; while DCP, anhydrous and lactose were comparable.



Table 4A

Summary of Low Drug Loading Dry Granulations made with  
Different Diluents

Lot#	1	2	3	4
Drug Form	A	A	G	M
Diluent	DCP, anhyd.	DCP, dihyd.	MCC	Lactose
Avg Slug Weight	1480 mg	1500 mg	1503 mg	1498 mg
Avg Slug Compression Force	39 kN	43 kN	18 kN	24 kN
Avg Slug Hardness	13 kP	11 kP	13 kP	13 kP
Avg Slug Thickness	0.132"	0.137"	0.184"	0.173"
Dry Granulation Density (g/cc)				
As Is	0.89	0.84	0.51	0.55
Tapped (2000x)	1.19	1.04	0.68	0.78
Carr's Index	26%	18%	25%	30%

Table 4B

Summary of High Drug Loading Dry Granulations made with  
Different Diluents

Lot#	1	2	3	4	5
Drug Form	A	A	G	M	F
Diluent	DCP, anhyd	DCP, dihyd.	MCC	Lactose	DCP, dihyd
Avg Slug Weight	1498 mg	1501 mg	1505 mg	1502 mg	1504 mg
Avg Slug Compression Force	28 kN	25 kN	16 kN	18 kN	8 kN
Avg Slug Hardness	12 kP	10 kP	9 kP	11 kP	9 kP
Avg Slug Thickness (in)	0.156	0.160	0.191	0.185	0.180
Dry Granulation Density (g/cc)					
As Is	0.67	0.69	0.53	0.53	0.63
Tapped (2000x)	0.96	0.92	0.71	0.75	0.86
Carr's Index	30%	25%	25%	29%	27%

- 5 The low drug loading dry granulations were compressed into tablets (target weight 750 mg) on the compaction simulator using 0.344" x 0.688" oval shaped tooling or 1/4" standard round concave (SRC) tooling.

Alternatively the high drug loading dry granulations were compressed into tablets (target weight 450 mg) on the compaction simulator using 0.262" x 0.531" modified capsule shaped tooling. Tablet hardness and friability data were generated for the tablets as described in Example 2. The tablet data are provided in Tables 4C and 4D for the low and high drug loading formulations, respectively. All tablets in Table 4D had the modified capsule shape.

As was previously shown in Example 2, the oval tooling produced friable tablets with the low drug loading granulations. Acceptable tablets were made with the same low drug loading granulations using SRC tooling. All the high drug loading granulations made good modified capsule shaped tablets, having friability values less than or equal to 0.5%. The lowest friability values for both the low and high drug loading granulations were obtained with MCC and lactose.

Table 4C

Tablet Data Summary for Low Drug Loading Dry  
Granulations made with Different Diluents

Lot#	1	2	3	4
Drug Form	A	A	G	M
Diluent	DCP, anhyd.	DCP, dihyd.	MCC	Lactose
Tooling Shape	Oval	Oval	Oval	Oval
Avg Tablet Weight (mg)	751	751	748	751
Compression Force	14kN	10kN	7kN	7kN
Avg Tablet Hardness (kP)	9.0	6.8	6.1	7.0
Avg Tab Thickness (in)	0.202	0.206	0.260	0.252
Friability (%)	Broken tablets	Broken tablets	1.30	Broken tablets
Tooling Shape	SRC (1/2")	SRC (1/2")	SRC (1/2")	SRC (1/2")
Avg Tablet Weight (mg)	747	751	752	752
Compression Force	10kN	10kN	9kN	10kN
Avg Tablet Hardness (kP)	5.8	6.2	5.3	7.5
Avg Tab Thickness (in)	0.195	0.198	0.243	0.236
Friability (%)	1.30	0.94	0.78	0.53

Table 4D

Tablet Data Summary for High Drug Loading Dry  
Granulations made with Different Diluents

Lot#	1	2	3	4	5
Drug Form	A	A	G	M	F
Diluent	DCP, anhyd.	DCP, dihyd.	MCC	Lactose	DCP, dihyd.
Avg Tablet Weight (mg)	448	454	453	452	452
Compression Force	5kN	5kN	5kN	4kN	4kN
Avg Tablet Hardness (kP)	6.2	5.2	5.8	5.8	7.0
Avg Tablet Thickness (in)	0.218	0.222	0.250	0.248	0.229
Friability (%)	0.50	0.49	0.41	0.28	0.31

5

Example 5Effect of Different Disintegrants and Tooling Types

The effect of different disintegrants on dry granulation tablets was investigated with high drug loading formulations for 250mgA, 500mgA and 600mgA doses using different modified capsule, oval and modified oval tablet tooling, respectively. Azithromycin form M was blended with disintegrants, sodium starch glycolate (Explotab) or crospovidone (PVP-XL) (Polyplasdone® XL).

10

The same long blend method and testing procedures as set forth in Example 2 were used.

The high drug loading formulation contained 58.2 wt% azithromycin, 31.8 wt% dicalcium phosphate dihydrate, 4.0 wt% disintegrant and 6.0 wt% magnesium stearate. Slugs were made and tested for hardness (kP scale), as described in Example 2. The granulation results are shown in Table 5A. The two formulations resulted in good flowing dry granulations as indicated by Carr's Index values less than or equal to 26%.

Table 5A

Summary of High Drug Loading Dry Granulations made with Different Disintegrants

Disintegrant	Explotab	PVP-XL
Avg Slug Weight	1499 mg	1515 mg
Avg Slug Compression Force	34 kN	35 kN
Avg Slug Hardness	12 kP	13 kP
Avg Slug Thickness	0.161"	0.164"
Dry Granulation Density (g/cc)		
As Is	0.67	0.63
Tapped (2000x)	0.91	0.84
Carr's Index	26%	25%

15

Tablets were made on the compaction simulator to cover the azithromycin doses of 250mgA, 500mgA and 600mgA using the tablet weights of about 450mg, 900mg and 1080mg, respectively. To accommodate the change in tablet weight, different sized tablet tooling were used: 0.262" x 0.531 modified capsule for the 250mgA dose,

20

0.330" x 0.670" oval for the 500mgA dose and 0.406" x 0.750" modified oval for the 600mgA dose. The tablet data are shown in Table 5B. Acceptable tablets were made with the 250mg dose and tooling without

- 5 precompression. The larger tablets were too friable when made without precompression. Acceptable tablets were made with the oval or modified oval toolings when precompression was used.

- 10 Precompression involves using slight pressure to tap down the granulation prior to the final compression step during the tableting process. The type of disintegrant used in the formulation had little impact on the compaction properties of the final tablet based on the 250mgA tablet data.

Table 5B

Disintegrant	Explotab	PVP-XL
Dose (mgA)	250	250
Tooling Shape	Modified Capsule	Modified Capsule
Precompression	No	No
Avg Weight (mg)	451	450
Avg Compresssion Force (Or ACF)	5kN	5kN
Avg Hardness (kP)	4.5	4.9
Avg Thickness (in)	0.226	0.230
Friability (%)	0.33	0.25
Dose (mgA)	500	600
Tooling Shape	Oval	Modified Oval
Precompression	No	No
Avg Weight (mg)	899	1082
ACF	6kN	6kN
Avg Hardness (kP)	5.6	4.2
Avg Thickness (in)	0.280	0.282
Friability (%)	2.71	6.34
Dose (mgA)	500	600
Tooling Shape	Oval	Modified Oval
Precompression	3.5kN	1.5kN
Avg Weight (mg)	898	1082
ACF	9kN	12kN
Avg Hardness (kP)	7.4	9.2
Avg Thickness (in)	0.275	0.268
Friability (%)	0.50	0.34



Example 6Effect of Tablet Shape and Drug Loading

The effect of tablet shape on dry granulation tablets was investigated with both low and high drug loading formulations using azithromycin form J. Both formulations were formulated with the same ingredients; only the percentage of drug and diluent was changed in the two formulations. The long blend method and testing procedures, set forth in Example 2, were used.

- 5 The low drug loading formulation contained 35.2 wt% azithromycin, 54.8 wt% dicalcium phosphate anhydrous, 4.0 wt% croscarmellose sodium, and 6.0 wt% magnesium stearate. The high drug loading formulation contained 58.2 wt% azithromycin, 31.8 wt% dicalcium phosphate
- 10 anhydrous, 4.0 wt% croscarmellose sodium, and 6.0 wt% magnesium stearate. Slugs were made as described in Example 2. The results for the low and high drug loading granulations are shown in Tables 6A. The Carr's Index was less than or equal to 28% for both granulations.

20

Table 6A

Summary of Azithromycin Form J Dry Granulations

Drug Loading	Low	High
Avg Slug Weight	1500 mg	1501 mg
Avg Slug Compression Force	41 kN	18 kN
Avg Slug Hardness	14 kP	11 kP
Avg Slug Thickness	0.134"	0.166"
Dry Granulation Density (g/cc)		
As Is	0.87	0.67
Tapped (2000x)	1.12	0.93
Carr's Index	22%	28%

Tablets were made on the compaction simulator using different shaped tablet tooling. Both the 0.344" x 0.688" oval tooling and the 0.262" x 0.531 modified capsule tooling were used for each formulation.

- 5 Additionally the 1/2" standard round concave (SRC) tooling was used for the low drug loading formulation as described in Examples 2 and 4. The tablet data are shown in Table 6B.

- 10 The oval shaped tablets with the low drug loading formulation broke during friability testing. The round shaped 1/2" SRC tablets using the low drug loading formulation produced tablets with improved friability of 1.46%. The same low drug loading granulation resulted in acceptable modified capsule shaped tablets with good  
15 friability. The high drug loading granulation resulted in acceptable tablets for both the modified capsule shape and the oval shaped tablets. The results indicate that tablet shape can be an important consideration. When using the low drug loading formulation, the  
20 modified capsule shaped tablet was the most preferred shape, followed by the SRC tablet shape; the oval shaped tablets were the most friable.

- By using a higher drug loading formulation, it was possible to produce an improved oval shaped tablet. The  
25 modified capsule shaped tablets had a lower friability value with the higher drug loading formulation, indicating that the higher percentage of azithromycin in the formulation improved the binding properties of the tablet.

Table 6B

## Tablet Data Summary for Different Tablet Shapes

Drug Loading	Low	High
Tooling Shape	Modified Capsule	Modified Capsule
Tooling Dimensions	0.262" x 0.531"	0.262" x 0.531"
Avg Weight (mg)	450	452
ACF	9kN	4kN
Avg Hardness (kP)	6.9	6.5
Avg Thickness (in)	0.193	0.229
Friability (%)	0.52	0.38
Tooling Shape	Oval	Oval
Tooling Dimensions	0.344" x 0.688"	0.344" x 0.688"
Avg Weight (mg)	747	750
ACF	15kN	10kN
Avg Hardness (kP)	9.1	10.2
Avg Thickness (in)	0.201	0.234
Friability (%)	Broken Tablets	0.71
Tooling Shape and Size	½" SRC	
Avg Weight (mg)	752	
ACF	9kN	
Avg Hardness (kP)	5.4	
Avg Thickness (in)	0.200	
Friability (%)	1.46	

Example 7Dry Granulation by Roller Compaction of Azithromycin

As an alternate process to slugging, a roller compaction study was performed to determine the effect of various roller compaction pressures on the dry granulation. The study also investigated the effect of drug forms on the roller compaction process.

A batch size of about 100g was made for each high drug loading formulation containing 58.2 wt% azithromycin, 31.8wt% dicalcium phosphate anhydrous, 4.0wt% croscarmellose sodium, and 6.0wt% magnesium stearate. The long blend method, set forth in Example 2, was used. Two different lots of form A were compacted using a Vector Roller Compactor (Model TF-Mini, Vector Corporation, Marion, IA) and were screened through a 20 mesh screen. The roller compaction parameters and the resulting dry granulation properties are shown in Table 7.

Table 7

## Granulation Properties and Roller Compactor Parameters

Lot #	1	2	3	4
Form A Lot	milled	milled	unmilled	unmilled
Dry Blend Density (g/cc)				
As Is	0.49	0.49	0.57	0.57
Tapped (2000x)	0.92	0.92	1.01	1.01
Carr's Index	47%	47%	44%	44%
Roller Compactor Parameters				
Roll Pressure Setting	850 psi	300 psi	500 psi	300 psi
Roll Speed	5 rpm	5 rpm	5 rpm	5 rpm
Screw Feed	7 rpm	7 rpm	7 rpm	7 rpm
Screened through	#20 mesh	#20 mesh	#20 mesh	#20 mesh
Dry Granulation Density (g/cc)				
As Is	0.55	0.60	0.64	0.66
Tapped (2000x)	0.91	0.90	0.92	0.92
Carr's Index	39%	33%	30%	26%

The Carr's Index values for the dry blend were extremely high, greater than 44%, indicative of poor flow. After roller compacting, the Carr's Index values were reduced, indicative of better flowing material.

5 Lower roller compaction pressures resulted in lower Carr's Index values.

The roller compaction process was evaluated for four different azithromycin forms, A, G, M and N. A batch size of about 300g was made for each high drug

10 loading formulation containing 55.76 wt% azithromycin, 32.24 wt% lactose, anhydrous, 10.0 wt% corn starch, and 2.0 wt% magnesium stearate:sodium lauryl sulfate (9:1). The drug, lactose, and corn starch were passed through a # 20 mesh screen and blended for 30 minutes in a Turbula

15 Shaker-mixer. The dry blend was then passed through a # 20 mesh screen and blended for another 30 minutes. Afterwards the dry blend was again passed through a # 20 mesh screen, combined with 1.5 wt% of lubricant and blended for 5 minutes. The dry blend was roller

20 compacted using a TF-Mini roller compactor (roller speed at 5 rpm, screw feed at 7 rpm, pressure of 850 psi). The compacted ribbons were passed through a # 20 mesh screen. The screened granulation was blended for 15 minutes, another 0.5 wt% of lubricant was added and

25 blended for an additional 5 minutes. The granulations were evaluated for flow using Carr's Index. All of the granulations had good flow; the Carr's Index values were less than or equal to 24%.

#0 size capsule shells were filled with about 470mg

30 of the granulation by hand. Data for the dry granulations and the capsules are given in Table 7A.

Table 7A  
Granulation and Capsule Properties

Lot #	1	2	3	4
Drug Form	A	G	M	N
Roller Compactor Parameters				
Roll Pressure Setting	850 psi	850 psi	850 psi	850 psi
Roll Speed	5 rpm	5 rpm	5 rpm	5 rpm
Screw Feed	7 rpm	7 rpm	7 rpm	7 rpm
Screened through	#20 mesh	#20 mesh	#20 mesh	#20 mesh
Dry Granulation Density (g/cc)				
As Is	0.66	0.67	0.62	0.65
Tapped (2000x)	0.86	0.86	0.82	0.84
Carr's Index	24%	22%	24%	23%
Avg. Capsule Fill Weight (mg)	450.1	434.2	409.8	446.8

Claims

We claim:

- 5 1. A pharmaceutical formulation, comprising:  
a tablet, sachet or powder for suspension which  
comprises
  - a) dry granulated particles of a non-dihydrate  
form of azithromycin; and
  - 10 b) optionally, one or more pharmaceutically  
acceptable excipients.
2. A pharmaceutical formulation in a tablet dosage  
form, wherein said tablet is produced by:
  - 15 (a) forming a blend of dry granulated particles of  
non-dihydrate azithromycin and at least one  
pharmaceutically acceptable excipient; and
  - (b) compressing said blend to form the  
azithromycin tablet.
- 20 3. A pharmaceutical formulation of Claim 2 further  
comprising the step of precompressing said blend  
prior to compressing said blend to form the tablet.
- 25 4. A pharmaceutical formulation of Claims 1, 2, and 3  
and comprising a tablet containing between about  
40%, by weight, to about 85%, by weight,  
non-dihydrate azithromycin.
- 30 5. A pharmaceutical formulation of Claims 1, 2, 3 and  
4 wherein the non-dihydrate azithromycin is  
selected from the group consisting of forms B, D,



E, F, G, H, J, M, N, O, P, Q, R, and mixtures thereof.

6. A pharmaceutical formulation of Claims 1, 2, 3, and  
5 4 wherein the non-dihydrate azithromycin  
comprises azithromycin form F.
7. A pharmaceutical formulation, comprising:
  - a) a capsule;
  - 10 b) dry granulated particles of a form of  
azithromycin selected from the group  
consisting of azithromycin forms D, E, F, G,  
H, J, M, N, O, P, Q, R and mixtures of  
non-dihydrate forms; and
  - 15 c) at least one pharmaceutically acceptable  
excipient
8. A pharmaceutical formulation of Claims 1-7 wherein  
the dosage of azithromycin is selected from the  
20 group consisting of 250 mgA, 500 mgA, 600 mgA and  
1000 mgA.
9. A pharmaceutical composition comprising dry  
granulated particles of a form of azithromycin,  
25 wherein said azithromycin form is selected from  
forms D, E, F, G, H, J, M, N, O, P, Q, R and  
mixtures of non-dihydrate forms, and at least one  
pharmaceutically acceptable excipient.
- 30 10. A dry granulated azithromycin particle, comprising:
  - (a) a form of azithromycin which is selected from  
forms D, E, F, G, H, J, M, N, O, P, Q, R and

mixtures of non-dihydrate forms; and  
(b) at least one pharmaceutically acceptable  
excipient.

- 5 11. A dry granulated azithromycin particle of Claims 9  
and 10 wherein said pharmaceutically acceptable  
excipients comprise a diluent, a disintegrant and a  
lubricant.
- 10 12. A dry granulated azithromycin particle of Claim 11  
wherein the diluent is selected from the group  
consisting of dicalcium phosphate dihydrate,  
microcrystalline cellulose, anhydrous lactose and  
lactose monohydrate.
- 15 13. A method of preparing an azithromycin  
pharmaceutical formulation, in a tablet, sachet or  
powder for suspension dosage form, comprising:
- 20 a) forming a blend of non-dihydrate azithromycin  
and at least one pharmaceutically acceptable  
excipient;
- b) compressing the blend to produce a  
compressed material;
- 25 c) milling the compressed material to produce  
granules;
- d) processing the granules into a tablet, a  
sachet or a powder for suspension.
- 30 14. A method of preparing an azithromycin  
pharmaceutical formulation, in a capsule dosage  
form, comprising:
- a) forming a blend of a non-dihydrate

- azithromycin, wherein said non-dihydrate  
azithromycin form is selected from  
azithromycin forms D, E, F, G, H, J, M, N, O,  
P, Q, R and mixtures of non-dihydrate forms,  
5 and at least one pharmaceutically acceptable  
excipient;
- b) compressing the blend to produce a  
compressed material;
- c) milling the compressed material to produce  
10 granules;
- d) processing the granules into a capsule.
15. A method of Claims 13 and 14 further comprising the  
step of blending at least one pharmaceutically  
15 acceptable excipient with the granules to form a  
blend prior to forming the dosage form.

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International Application No

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A. CLASSIFICATION OF SUBJECT MATTER  
 IPC 7 A61K9/20 A61K31/70

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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